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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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☑ *Additional inventors are being named on the* 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Resonant Cavity Biosensor

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages*	11	☐ CD(s), Number	
☐ Drawing(s) *Number of Sheets*		☐ Other (specify)	
☐ Application Data Sheet. See 37 CFR 1.76			

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

		FILING FEE AMOUNT ($)
☑ Applicant claims small entity status. See 37 CFR 1.27.		
☐ A check or money order is enclosed to cover the filing fees		
☑ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:	023255	$80.00
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE David Bergstein Date 03/19/2003

TYPED or PRINTED NAME David A. Bergstein REGISTRATION NO. *(if appropriate)*

TELEPHONE (617) 353-5887 Docket Number: BU02-86

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Additional Page

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Docket Number	BU02-86

INVENTOR(S)/APPLICANT(S)		
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Bennett B	Goldberg	Newton, MA 05246

Number 2 of 2

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Title: Resonant Cavity Biosensor

Non-confidential brief description of usefulness:
The biosensor will detect interactions between target biomolecules in solution and probe biomolecules fixed to a surface. The biosensor will create images of the surface in real-time that indicate where interactions have taken place. Different probe molecules may be laid out on the surface in an array format as a protein chip, DNA chip, or immunoassay. It may be possible then to monitor thousands, or hundreds of thousands of different biomolecule interactions simultaneously in real time. This detection would provide critically needed information for tasks such as high throughput drug screening, bio-warfare agent detection, and medical diagnosis. Such a detection method would also provide enormous help to genomics studies, proteomic studies, and bioresearch in general.

One-page description of usefulness:
Fields as diverse as bioresearch, ecology, medicine, pharmacology, and bio-weapons detection are finding a critical need for biomolecule interaction affinity sensing [Schena 1999] [Casagrande 2002]. Biomolecule affinity sensing measures the affinity various biomolecules have for each other including DNA, RNA, protein, and small molecules [Gauglitz 2000]. High throughput methods offer the greatest potential. They can speed up a bio-researcher's work, help a pharmaceutical company screen faster for candidate drugs, help a doctor screen more accurately for diseases, or help a bio-warfare detector identify agents more accurately by obtaining the greatest amount of information quickly with minimal effort [Schena 1999].

DNA arrays and protein arrays, commonly called DNA or protein chips, are two technologies used for biomolecule affinity sensing that have sparked a remarkable amount of interest and are starting to take root in fields of genomics and proteomics. The principle behind both is to start with a substrate covered with a bio-layer of material such as single stranded DNA or protein that acts as the probe, introduce the probe surface to a solution containing target molecules, and detect target-probe binding. Typically the probe surface is patterned in an array where each element contains a different biomolecule, such as a DNA chip with a grid pattern where the DNA in each location is of a different sequence. Arrays may have anywhere from a few different probes patterned on their surface to half a million different probes, truly earning the name high throughput [Schena 1999].

In general, the user will know where on the surface the different probes have been patterned and will want to know at which of those locations binding has occurred, and ideally what the affinity for that interaction is. One example could be a bio-researcher who wants to understand what DNA sequences bind to a particular protein that has been purified. Using a chip with an array of likely DNA candidate sequences, the bio-researcher can introduce the purified protein and determine its affinity for the different DNA sequences that are fixed to the chip surface. The bio-researcher might even gather kinetics information by observing the rate that the binding took place and the rate that the binding disassociates under wash or heating. Another example might be a medical doctor who wants to determine expression level of particular RNA sequences in a patient's cell. The doctor can take a sample from a patient, purify out the RNA content, and introduce it to a carefully designed RNA chip surface. The target RNA will tend to bind to the short probe RNA strands on the chip where the sequence matches strongly. The chip could be carefully designed to give unique and clearly identifiable patterns to indicate high expression levels of the RNA sequences the doctor is interested in [Schena 1999]. Such information could help a doctor understand what is going on inside the cell and thereby diagnose a patient with greater accuracy. Anther example might be a bio-warfare detector that would have antibodies for the different bio-warfare agents on its surface. The surface would be exposed to a water sample to be tested, or a solution in which air molecules have been dissolved. Dissolved molecules would bind selectively to the antibody surface and could indicate if a hazard exists [Casagrande 2002].

In each of the above examples, affinity detection is a critical part of the process. Present affinity sensors tend to suffer from one of the following: either it is not high throughput, it is not real-time, involves a labeling process that may be difficult or impossible, or requires the use of a metal surface incompatible with many surface chemistries [Hieftje 1998]. Our proposed invention offers a high throughput real-time label-free detection technique that would use a dielectric surface and could be used for any one of the above applications and many more.

Description of Invention

General Purpose:
The purpose of this invention is to detect interactions between target biomolecules and probe biomolecules. The probe molecules will be attached to a surface, such as a DNA chip or protein chip. The target molecules will be in a solution such as water or buffer. The detection will be label-free meaning that labels do not need to be added to the target molecules. The detection can be monitored real-time, meaning that the binding information is being analyzed and displayed as fast as it is being collected. This rate is generally faster than the rate of binding which will allow the user to extract kinetics information such as the dissociation constant for the reaction.

Technical Description:
The principle of our detection method relies on the use of a resonant cavity. The resonant cavity is formed from two partially reflecting mirrors with their reflecting sides facing each other (Fig. 1). Light enters the cavity through one of the mirrors and generally reflects back from the two mirror structure, except at or nearby particular wavelengths where the incident light will excite the resonant condition within the cavity, and transmit through. With highly reflecting mirrors, the resonant condition is sharp, and light only transmits at the particular wavelengths exciting the resonant condition [Saleh 1991]. This property of the resonant cavity is used often in optics to very narrowly filter at particular frequency.

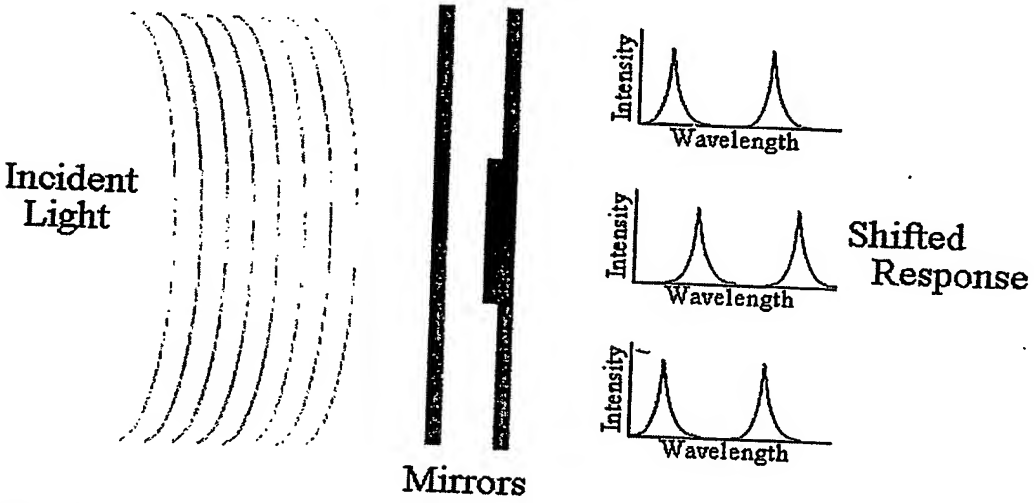

Fig. 1 The mirrors are placed parallel to one another with their reflecting surfaces facing each other to form the cavity. Transmission peaks can be observed at particular wavelengths where the resonant condition of the cavity is excited. Parameters such as the optical path length in the cavity, and the phase response of the mirrors will affect the resonant condition of the cavity, and hence the wavelength where the transmission is peak.

Our idea is to observe at what wavelength the resonant condition is satisfied and use this to determine if a change in the cavity due to binding has occurred. We propose that the probe surface be fabricated on the surface of one of the mirrors (Fig. 2). Slight changes in the cavity, such as the build up of an addition bio-layer on the chip surface will cause a relatively large shift in the resonant wavelengths of the cavity. This build up will occur as target molecules leave a

target rich solution in the cavity and bind to the probe surface. We can then sweep the incident light through a range of wavelengths and observe the transmission peaks at the other side to determine at which wavelengths the resonant condition is satisfied. As binding occurs between target molecules in solution and the probes bound to the mirror surface, the resonant condition of the cavity will change, and the wavelength of an observed transmission peak will shift. We can detect this shift and conclude that binding has occurred.

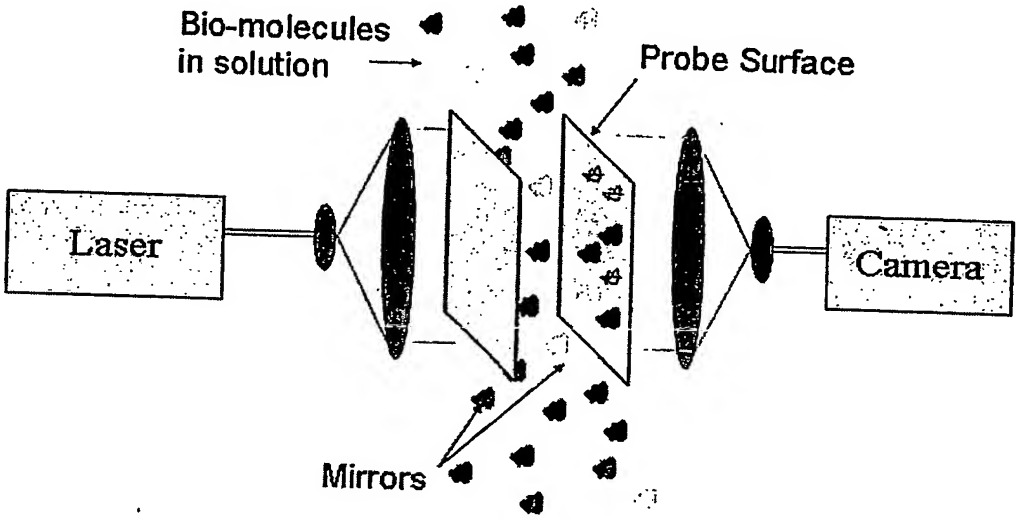

Fig. 2 A tunable laser will sweep through a range of wavelengths. Expanding optics will expand and collimate the beam to illuminate the entire cavity. A target rich solution will flow between the mirrors which also form the flow cell. The probe surface will be fabricated onto one of the mirrors. Condensing optics will image the probe surface onto the sensor array of a digital camera.

This detection can be done in a massively parallel fashion to yield a high throughput technique. The detector for determining the transmission intensity could be a detector array such as a CCD or other such sensor array. The probe surface can then be divided into an array of spots such as is done with DNA or protein chips. The mirror distances will be close enough such that each spot on the array may act as the mirror of its own resonant cavity, and small groups of pixels or individual pixels on the camera may act as a detector for that resonant cavity. Camera arrays can be quite large and dense, and optics may be used to image the transmitting light as necessary to fit on the sensor array. DNA chips have been fabricated using photolithography to create as many as half a million different spots in an array format on a chip only a few cm's in size. We will have to keep our detected spot sizes large enough that each can act as its own resonant cavity. This will depend on the wavelength of light, the distance between the mirrors, and the tolerance on keeping the mirrors parallel. These limiting factors on the detection spot size indicate that the potential throughput of our device will be very high.

The mirror surfaces used to create the resonant cavity can be inexpensive and compatible with most biomolecule array surface chemistries. The mirrors may be distributed Bragg reflectors that are constructed from alternating layers of dielectric materials such as Si and SiO_2. Layers can be easily and inexpensively fabricated using different techniques such as those developed by Dr. Selim Ünlü at Boston University. The greatest benefit of using distributed Bragg reflectors

composed of dielectric materials is their compatibility with biomolecule surface chemistries. Most DNA and protein chips to date are fabricated on glass microscope slides [Schena 1999]. We may include a final layer of SiO_2 on our layered reflector making it no more difficult to fabricate a DNA or protein chip on our reflector as it is to fabricate one on a typical glass surface. Additionally, SiO_2 surfaces can be cleaned and re-used without damage [Goddard 1993]. Alternatively, if fabricated cheaply enough, the reflectors may simply be disposable.

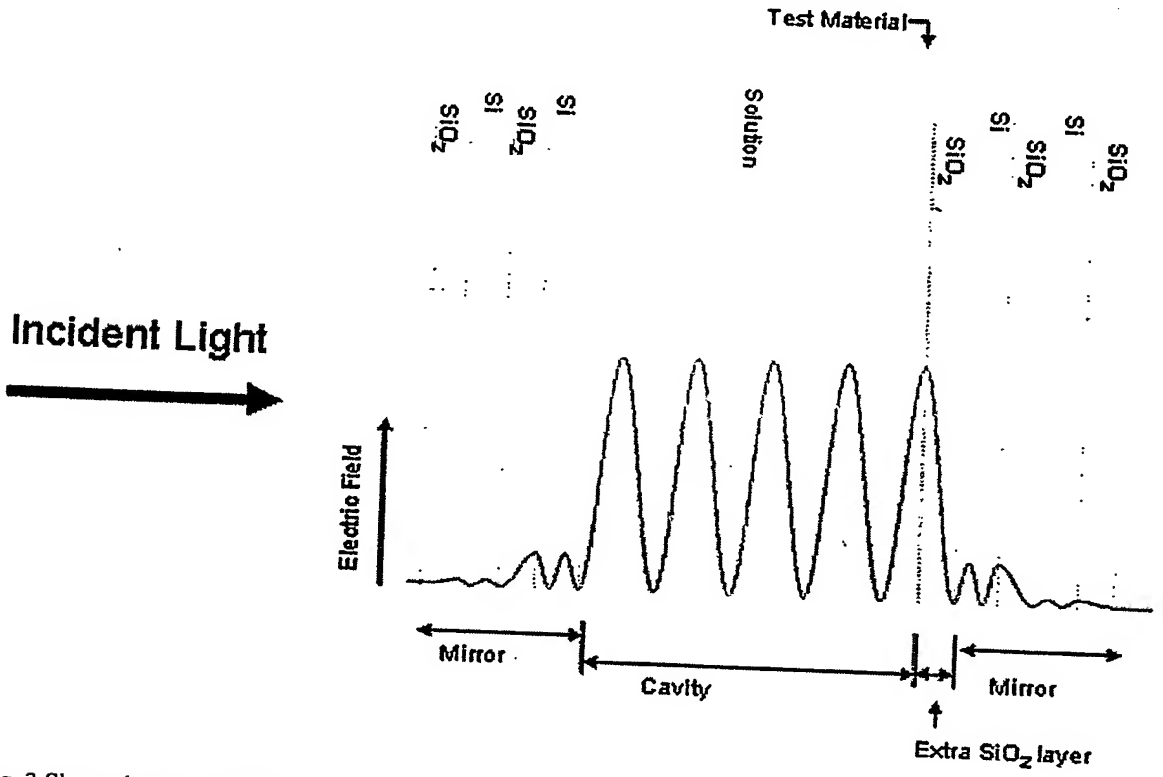

Fig. 3 Shown here is the electric field profile for the cavity when the resonance condition is satisfied. Note the large field within the cavity due to the resonance. The extra SiO_2 layer thickness can be chosen to maximize the field strength at the probe surface, which lies between the SiO_2 layer and the target rich solution.

A final layer of SiO_2 may also play a more critical role by enhancing the sensitivity of the detection. As stated earlier, small changes in the resonant cavity material can cause a large shift in the resonant wavelength. We may model the change caused by binding as a change in optical index of a thin layer directly adjacent to the probe layer. As the thin layer changes refractive index, the resonant condition will change and the resonant wavelength will shift. The optical field within the cavity will form a standing optical wave with peaks and nodes (Fig. 3). If the optical field is strong in the region of the layer where the index is changing, the change will greatly affect the resonant condition (Fig. 4). If the optical field is weak in the region of changing index layer, the shift in resonant wavelength will be small (Fig. 4). The thickness of the final SiO2 layer can be carefully chosen to maximize the sensitivity of the detection by ensuring that the optical field is strong in the region of the probe layer for the wavelengths in the neighborhood of the expected resonance wavelength.

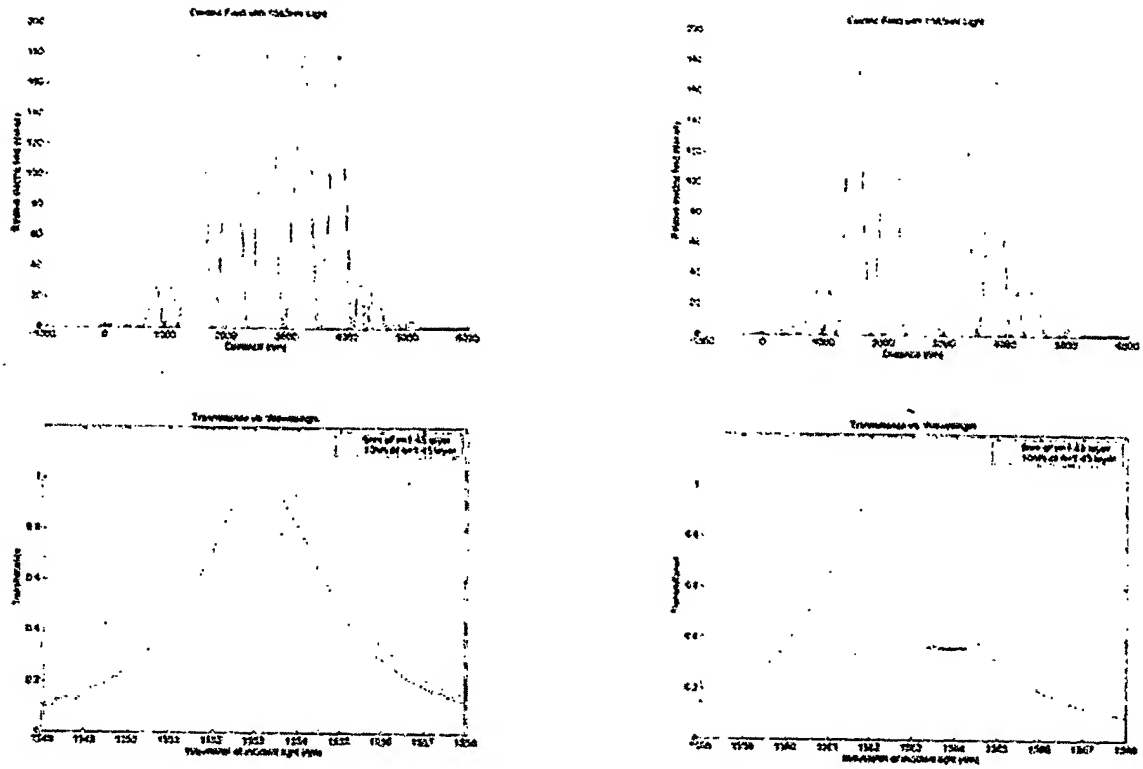

Fig. 4 Here simulation shows the effect of the SiO_2 layer thickness can be seen. The cavity is assumed to be filled with buffer (n=1.33) and the probe surface is a 5nm thick material of n=1.45 and changing to a surface 10nm thick with binding. With an extra SiO_2 layer thickness of around 250nm, the field is maximized at the probe surface and the wavelength shift resulting from a 5nm build up of material (n=1.45) at the probe surface is easily seen. With a SiO_2 layer thickness of around 500nm, the field is minimized at the probe surface and the wavelength shift is hard to discern.

Sensitivity may also be enhanced by increasing the reflectivity of the mirror surfaces. Increasing the reflectivity of the mirrors sharpens the resonance condition. The reflectivity of the mirrors can be easily improved by adding more alternating dielectric layers (Fig. 5).

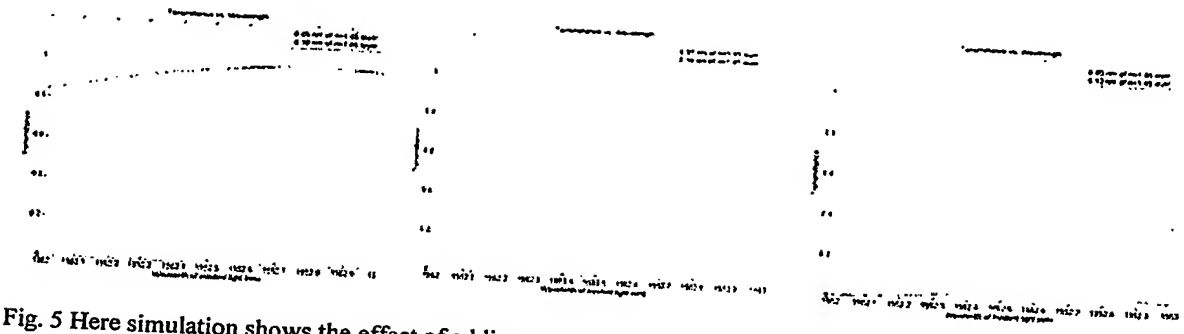

Fig. 5 Here simulation shows the effect of adding more alternating dielectric layers to the mirrors. The solution is again assumed to be n=1.33 and the material is assumed to be n=1.45. The probe layer here is 0.05nm and the target-probe layer thickness is 0.10nm. With mirrors formed from 2 periods of low and high dialectic materials (LHLH) the sensitivity is low as can be seen in the left plot. The center shows the improved sensitivity with 3 periods of material forming the mirrors (LHLHLH). And the right plot shows the high sensitivity capability when using 4 periods of material (LHLHLHLH).

Advantages over existing technology:

Key features that are sought in affinity sensors include high throughput, high sensitivity, a chemically compatible surface, real time analysis, affordability, and ease of use [Hieftje 1998]. While many other technologies meet some of these criteria, none presently meet all of these criteria. Our invention appears to be able to meet all these criteria offering a clear advantage over other technologies. Some other methods for detection are described below.

Fluorescent tagging the target molecules is without doubt the most popular method for detection with DNA or protein arrays. A variation of this is to fluorescently tag antibodies that selectively bind to the target molecules. After binding is thought to have occurred, the chip surface is laser scanned and the fluorescence from each spot is recorded. The result is a fluorescence image that can be compared with a map of probe locations on the chip. The trouble with direct fluorescent labeling is that it can be difficult or impossible to add the tags and the tags may modify the binding properties. Using tagged antibodies can be troublesome as well as it may be difficult or impossible to attain the needed antibodies. Other methods of tagging include the use of radioactive tags or gold tags where the presence of gold is detected using electric circuits. Both suffer as well from the often difficult or impossible attachment of the tag. Protein detection by tagging is particularly susceptible to problems caused by the tag modifying the binding properties of the protein in unpredictable ways. All these tagging methods suffer additionally from the fact that binding cannot generally be monitored continuously in real time and hence kinetic information is largely lost.

Label-free techniques have gained a lot of interest since they avoid the problems associated with tagging. Surface plasmon resonance (SPR) is the most popular label-free method. There are a number of companies now offering off-the-shelf SPR scanners (BIOS-1 by ASI AG, Spreeta by TI, IBS by Xantech, Plasmoon by BIOTUL [Gauglitz 2000]; FLEX CHIP by HTS Biosystems). One major downfall with SPR is that it requires the biomolecules to be affixed to a metal surface, typically gold. Many of the surface chemistries developed for DNA or protein arrays are incompatible with a metal surface and tend to be developed for SiO_2 microscope slides which often work much better than the gold surfaces [Goddard 1993].

Less popular label-free detection techniques include waveguide techniques and acoustic techniques. Both tend to suffer from the difficulty in scaling up to become high throughput. There is one waveguiding technique that has gone far in development and use. It is incorporated into the IAsys® biosensor from Thermal Labsystems that its inventors have termed the resonant mirror, or RM technique [Goddard 1993][www.thermolabsystems.com]. The product has filled the niche of using dielectric surfaces and being able to provide real time information for kinetic analysis. Fluorescent tagging cannot provide kinetic analysis, and SPR requires a gold surface. IAsys has been used in a good deal of research to date and referenced hundreds of research articles [www.thermolabsystems.com]. However, the IAsys can only measure with one or two different probes simultaneously which is a severe drawback.

Reflectometric interference spectroscopy, named RIfS, uses thin-film interference to detect the presence of a bio-layer on a probe surface. RIfS is similar to our technique in that it is dependent on the reflective properties of a thin film modified by binding to an interaction layer. Though RIfS is different in that it doesn't use mirrors, uses only one dielectric layer, is based on reflectance, and uses fiber probes. RIfS does use dielectric materials as does ours. It has been shown that this method can detect with sensitivity comparable with other methods mentioned [Gauglitz 1996]. The fiber setup that is used with RIfS, however, severely limits the throughput of the detector.

The advantage of our detection method is that it offers a real time, high throughput technique that uses a dielectric surface and shows promise of being highly sensitive, affordable, and easy to use.

Possible variations and modifications:

- Use wavelength ranges other than IR
- Use light at an angle other than normal incidence
- Evaluate properties of transmitted light other than amplitude, such as polarization, phase, or wavelength
- Instead of sweeping wavelength continuously, could evaluate using a discrete set of wavelengths, including the possibility of evaluating transmittance or other property of light at a single wavelength
- Replace external cavity tunable laser with other tunable source including cheaper temperature tunable laser diode
- Use non-tunable source
- Use VCSEL array as source
- Modifications of the flow cell geometry
- Controlling the temperature in the flow cell or cavity
- Controlling either the electric field or magnetic field within the flow cell or cavity
- Dynamically controlling the size of the flow cell or cavity, such as expanding or contracting the cavity during a measurement
- Process frames by averaging, differentiating, or correlating frames or pixels
- Instead of using a photodetector array, could scan with a linear photodetector array, or scan with a single photodetector

- Could scan to a linear array photodetector or single photodetector using MEMs devices such as a MEMs micro mirror device.
- Fabricate biomolecule probe surface directly on photodetector surface that would be either re-usable or disposable

Features believed to be new:
Our technique is different from Surface Plasmon Resonance (SPR) techniques, waveguide techniques, and Reflectometric Interference Spectroscopy (RIfS) techniques in that we are observing the transmission of light through a resonant cavity where the incident light is normal to the surface, and where the light transmitting through the interaction surface is a propagating wave.

Surface Plasmon Resonance (SPR) techniques are based on exciting surface plasmons on a thin metal surface and detecting a change in the resonance angle or resonant wavelength for those surface plasmons as target molecules bind to probes on the opposite side of the metal layer and modify the surface plasmon resonant behavior. This is very different from our idea since we do not excite surface plasmons in metal to detect biomolecules. We use a resonant cavity where the light interacting with the molecules to be detected is a propagating wave.

Waveguide techniques rely on exciting resonant modes within a waveguide. The critical difference is that the light in a waveguide technique relies on total internal reflection at a boundary, and it is the non-propagating evanescent field that penetrates the biomolecule interaction surface and in turn affects the condition of the cavity. In our device we use a propagating field that transmits through the interaction layer. It should also be noted that the waveguide techniques observe a change in phase of totally reflected light, whereas we observe a change in intensity of transmitted light. Also unlike waveguide techniques, in our method the probe surface, target-rich solution, and binding process all occur within the cavity itself.

Our technique is different from the Resonant Mirror (RM) technique for the same reasons that it is different from the waveguide techniques. Namely, RM uses total internal reflection and an evanescent field. We use transmission and a propagating field. RM observes the phase of reflected light, while we observe the intensity of transmitted light.

The method that is closest to ours is Reflectometric Interference Spectroscopy (RIfS). Here light is reflected from a thin film and the phase between the two reflections (front surface and back surface) is compared. The measurement is done at the tips of fiber which are fed back to a spectrometer to analyze the wavelength response. The intensity of light reflecting from the thin film will have a wavelength dependency on the thickness of the film. The probe surface is the back surface of the thin film and exposed to a target rich solution. As targets bind, the thickness of the thin film is modified, and the wavelength response shifts. One key difference is that we use a resonant cavity, relying on an infinite sum of repeated reflections within the cavity to form a sharp resonance peak in our wavelength response, while RIfS uses only two reflections and produces a broad response. RIfS also looks at light reflected back from the structure, not light that transmits through the biomolecule interaction layer and the target-rich solution. Another key difference is that we can evaluate an entire plane of probes in a chip format at once, while the spectrometer requirement of RIfS makes it impractical to evaluate many probe areas simultaneously [Gauglitz 1996].

Close or related patents:
The RM technique, which has been incorporated into Thermo Labsystem's IAsys biosensor, is similar. US Patent 4,857,273 was granted on Aug. 15, 1989 and covers their work. For the reasons given above, our idea is clearly different though related.

US patent 5,804,453 for the RIfS technique repeatedly refers to reflection and the use of a fiber. Our idea does not infringe since we use mirror structures, excite a resonant condition, do not use a fiber, look at transmission, and propagate the field though the target rich solution.

Problem solved:
To make a label-free, high throughput, parallel biomolecule affinity detector that detects on a dielectric surface friendly to the biochemistry of DNA and protein chips, and which can be made cheaply and easy to use.

Possible uses:

- Scientific Instrumentation
- Medical Diagnostic Device
- Biological or Chemical Hazard Warning Device

Also see description of usefulness above.

Disadvantages or limitations:
There may be a few disadvantages to our system compared with others. The most important factor may be cost. Our present configuration calls for an InGaAs detector array and an external cavity tunable laser, each of which costs around ten thousand dollars. Another disadvantage may be that in our present configuration, the cavity thickness is limited and must be on the order of hundreds of microns or less. It is unclear yet whether this would pose a problem or not.

State of development:
Simulations have been performed with encouraging results. Much of the needed instrumentation needed for experiment has been identified and borrowed. Experimentation has begun and resonant curves for a thin silicon wafer have been correctly identified.

Prospective commercial interest:
There is considerable commercial interest for this class of techniques. Analysts predict that the biochip market in will go from its $400 million mark in 2000 to $1 billion by 2005 [Lewotsky 2002]. The protein chip market in particular is perhaps a better aim since it requires label-free detection far more than the DNA chip market where fluorescence is a strong competitor. The protein chip market alone is expected to grow from $44 million in 2000 to $490 million in 2006 [Lewotsky 2002]. This up-and-coming biochip industry will require detection methods to go along with chip usage. Our invention would provide a means of detection for biochip users.

Portable biomolecule affinity detectors for individual use may also be a possibility using our method of detection. This would require bringing down the cost and size of the laser as well as the cost of the detector array. This may be accomplishable with some of the possible

modifications listed early, such as using a tunable laser diode source instead of the external cavity tunable source, using a single photodetector with scanning MEMs devices, or relying on possible advances in the photodetector field over the next few years. Creating a cheap portable biomolecule affinity detector for individual use could open up an entirely new market with unimaginable potential.

List of licensees:
There are an ever-growing number of biotech companies becoming involved in the biochip industry at all levels. Any one of these companies may be interested in developing this detection technology and could serve as a potential licensee.

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